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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/934,300	08/21/2001	Todd Lewis Talarico	35780/233666 (5780-5)	8297

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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/934,300	TALARICO ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *4/15/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 04/15/04 in response to the non-final Office Action mailed 12/19/03. With this, Applicants have amended the specification.

Status of Claims

2) No claims have been amended via the amendment filed 04/15/04.

Claims 12-19 are pending and are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

5) The objection to the drawings made by the Draftsperson as indicated in PTO-948 attached to the Office Action mailed 07/01/03 and maintained in paragraph 6 of the Office Action mailed 12/19/03, is withdrawn in light of Applicants' submission of formal drawings filed 04/15/04.

Rejection(s) Maintained

6) The rejection of claims 12-16 and 18 made in paragraph 19 of the Office Action mailed 12/19/03 under 35 U.S.C. § 102(b) as being unpatentable over Woghiren *et al.* (*Bioconj. Chem.* 4: 314-318, 1993) in view of Miles *et al.* (*Art. Cells Boold Subs. Immob. Biotech.* 25: 315-326, 1997 - Applicants' IDS) or Iwashita *et al.* (*Biomat. Art. Cells Art. Org.* 16: 271-280, 1988, already of record) or Rausch *et al.* (US 5,084,558 - Applicants' IDS) and Katsunuma *et al.* (US 4,229,571) or JP 53038617 ('617), is maintained for reasons set forth therein and herebelow. See the following paragraph.

7) The rejection of claims 17 and 19 made in paragraph 20 of the Office Action mailed 12/19/03 under 35 U.S.C. § 103(a) as being unpatentable over Woghiren *et al.* (*Bioconj. Chem.* 4: 314-318, 1993) as modified by Miles *et al.* (*Art. Cells Boold Subs. Immob. Biotech.* 25: 315-326, 1997 -

Applicants' IDS) or Iwashita *et al.* (*Biomat. Art. Cells Art. Org.* 16: 271-280, 1988, already of record) or Rausch *et al.* (US 5,084,558 - Applicants' IDS) and Katsunuma *et al.* (US 4,229,571) or JP 53038617 ('617) as applied to claims 16 and 18 above, and further in view of Feola *et al.* (US 5,439,882, already of record), is maintained for reasons set forth therein and herebelow.

Applicants contend that a *prima facie* case of obviousness requires some suggestion to combine the cited references to arrive at the claimed invention and a reasonable expectation of success in such a combination. Applicants state that the claimed invention in the instant case is a method of preparing a chemically modified hemoglobin that is substantially free of contaminants comprising dissolving an aPEG in a solvent in which the aPEG is stabile, filtering the aPEG solution to substantially reduce the level of contaminants, and combining the filtered aPEG solution with a hemoglobin solution. Applicants point to pages 15-17, Example 4, and Tables 2-3 of the instant specification and submit that significant reductions in contaminants present in the chemically modified hemoglobin solution result from using a filtered aPEG solution. With regard to the Office's statement that the motivation to combine the cited references to arrive at the claimed methods arises from the desirability of producing a safer, non-toxic hemoglobin solution for use a therapeutic, Applicants allege that this reasoning is insufficient to establish a motivation to combine the references. Applicants assert that even if combined, the references would not allow one of skill in the art to produce the claimed invention. Applicants further submit that in contrast to the teachings of Woghiren *et al.*, the present invention requires dissolving the aPEG in a solvent in which it is stable, filtering the solution to substantially reduce bioburden and endotoxin contaminants, and then using the filtered aPEG solution to modify hemoglobin. Applicants re-state that the filtration methods of Woghiren *et al.* do not substantially reduce contaminants and that the reference does not teach or suggest filtering the final PEG-SS-4TP solution prior to using it to modify papain. Applicants contend that the modified papain solution is purified to substantially reduce contaminants only after the chemical modification has occurred.

With regard to the disclosure of Katsunuma *et al.*, Applicants state that Katsunuma's compositions and methods are directed to a glucocorticoid sparing factor. JP 53038617 is said to teach a method for preparing an inactivated hepatitis B vaccine. Applicants acknowledge that both references teach the use of gel filtration and column chromatography for the purification and

separation of compositions of interest, but argue that these references are not directed to hemoglobin solutions or suggests filtering an aPEG solution.

With regard to the disclosure of Miles *et al.*, Applicants state that the reference teaches an HPLC-based method for the quantitation of residual alpha-carboxymethyl, w-carboxymethoxyl POE in chemically modified hemoglobin solutions. Applicants readily admit Miles' acknowledgment that the removal of residual chemical modification reagents is crucial to the production of a safe product. Applicants state that Iwashita *et al.* teach compositions and methods directed to a pyridoxalated hemoglobin-POE conjugate, wherein the modified hemoglobin is purified by repeated ultrafiltrations of the final product. Applicants contend that Rausch *et al.* disclose a cross-linked, substantially endotoxin-free hemoglobin solution and a method for producing the same. Applicants allege that the methods of Rausch *et al.* comprise several filtrations of the unmodified hemoglobin solution in order to remove endotoxin contaminants prior to cross-linking with glutaraldehyde. Applicants assert that none of these references teach or suggest using a stable, filtered aPEG solution to modify hemoglobin. Applicants allege that none of the cited references 'teach or suggest dissolving an aPEG in a solvent in which it is stable and then filtering the aPEG solution to substantially reduce the level of contaminants prior to using it to modify hemoglobin, as required by the claimed invention. Applicants conclude that there is insufficient motivation to combine the cited references to obtain the claimed invention and that a *prima facie* case of obviousness has not been established. Applicants then argue that even if combined, the references would not allow one of skill in the art to arrive at the claimed invention.

With regard to Feola *et al.*, Applicants state that the reference teaches the use of a 0.2 micron Posidyne® filter to remove contaminants from an extracted, unmodified hemoglobin. Applicants submit that Feola does not teach or suggest using an aPEG to chemically modify a hemoglobin solution, and do not suggest using any filter to remove contaminants from the aPEG solution. Applicants point to page 316 under 'Materials and Methods' of Miles *et al.* and state that it is the pyridoxylated hemoglobin-POE conjugate samples, and not the POE solutions that were filtered using a 0.45 micron filter. Applicants state that Miles *et al.* do not suggest filtering POE or any aPEG solution using a filter of any size. Applicants assert that the mere fact that Feola *et al.* use a 0.2 micron filter to remove contaminants from stroma hemoglobin solution is no indication that one

of skill in the art would have been motivated to dissolve an aPEG in a solvent in which it is stable, filter the aPEG solution through a filter of any type to substantially reduce contaminants, and then use the filtered aPEG solution to modify hemoglobin.

Applicants state that Woghiren *et al.* teach a thiol-protected activated aPEG and a method of using it for the modification of cysteine-containing proteins. Applicants state that Woghiren *et al.* do not teach or suggest chemically modifying hemoglobin. Applicants further state that the production of PEG-SS-4TP aPEG requires several intermediate reactions in order to produce the final, desired aPEG, PEG-SS-4TP. Applicants acknowledge that at each of the steps, the reaction products are separated from the residual chemical reagents by filtration through Sephadex G-25, but argue that Woghiren *et al.* do not teach or suggest that this filtration step is intended to or actually does substantially reduce bioburden and endotoxin contaminants. Applicants point to page 315, right column of Woghiren *et al.* and submit that Woghiren *et al.* expressly state that the reaction products are only 'partially purified' by Sephadex G-25 indicating that the filtration step does not substantially reduce the level of contaminants, as required by the present invention. Applicants argue that in the final synthetic step, the PEG-SS-4TP, is 'isolated' by gel filtration as before, frozen, evaporated to dryness using a vacuum concentrator, and then mixed with papain protein solution to obtain PEG-papain solution. Applicants state that the PEG-papain solution is purified by HPLC and high-performance gel filtration chromatography. Applicants submit that contrary to the claimed methods, the final aPEG solution that is used to modify papain is not filtered prior to use. Applicants allege that there is no suggestion in the reference that PEG-SS-4TP could be successfully used to modify hemoglobin.

Applicants' arguments have been carefully, considered, but are non-persuasive. Applicants are reminded that the various references were applied in 35 U.S.C. § 103 rejection(s) as opposed to 35 U.S.C. § 102 rejection(s). If the reference taught what is claimed, each reference would have been applied under a 35 U.S.C. § 102 rejection. Applicants have failed to fully address the teachings of the various references that were cited in the body of the rejection(s).

Contrary to Applicants' allegation, Woghiren *et al.* taught that the excess of tosyl chloride was conveniently eliminated from the activated product in the 'gel filtration **purification** step' [Emphasis added]. Woghiren *et al.* further expressly taught that the 'final product', PEG-SS-4TP,

'gave a single peak' when analyzed by LDMS mass spectrometry (see page 316, left column; and Figure 2A) thus indicating that the activated final PEG product was in fact purified. Contrary to Applicants' contention and as clearly set forth in paragraph 19 of the Office Action mailed 12/19/03, Woghiren *et al.* taught a method of preparing a chemically modified protein solution which involves the step of activating PEG into a stable reagent. The activated PEG was dissolved in a solvent, such as, methanol or pyridine; and the solution was subjected to gel filtration for the purpose of purification. The fourth sentence in the left column on page 315 explicitly states that the tosyl-PEG 'was purified from tosyl chloride by passage through Sephadex G-25'. The first full paragraph in the left column on page 315 states that the PEG-thioacetate was 'purified using Sephadex G-25 as above'. Even Woghiren's partial purification meets the recitation in the instant claims: 'substantially free of contaminants'. The resultant PEG solution was combined with a protein solution. Thus, contrary to Applicants' contention, Woghiren filtered the aPEG solution before combining with the papain protein (see abstract; page 314, left column; and 'Experimental Procedures', especially on page 315). That the prior art gel filtration includes or involves at least one filter is implicit from the teachings of Woghiren *et al.* in light of what was well known in the art. For instance, Katsunuma *et al.*, or the JP '617 patent taught that gel filtration is effected through a filter (see claim 5 of Katsunuma *et al.* and the abstract of the '617 patent). That the process of filtering reduced the levels of contaminants in the prior art method and rendered the solution substantially free of contaminants is implicit from the teachings of Woghiren *et al.* Applicants ignore or fail to address Woghiren's teaching of dissolving the activated PEG in a solvent, such as, methanol or pyridine, yet allege that the reference does not teach dissolving an aPEG in a solvent in which the aPEG is stabile. Furthermore, Woghiren *et al.* do not have to teach filtering the solution 'to substantially reduce bioburden and endotoxin contaminants' since such limitations are not present in the instant claims. Contrary to Applicants' statement, Woghiren *et al.* did teach filtering the final PEG-SS-4TP solution prior to using it to modify papain by passing it through filter-containing Sephadex columns.

The references of Katsunuma and JP 53038617 were applied in the rejection to document that gel filtration is effected through a filter and to show that Woghiren's process of filtering impliedly involves the filtering process which process indeed reduces the levels of contaminants and renders the aPEG solution substantially free of contaminants. The Office Action did not mention the

terms, glucocorticoid sparing factor and inactivated hepatitis B vaccine. As Applicants readily acknowledge, Miles teaches that the removal of residual chemical modification reagents from the aPEG solution is crucial to the production of a safe product. Miles *et al.* taught the use of PVDF syringe filters for filtration (see page 316). Miles *et al.* identified the need in the art for the safe use of purified hemoglobin solutions as therapeutics in humans. Most importantly, Miles *et al.* taught a method of accomplishing it by linking to POE to prevent toxicity (see abstract). Miles *et al.* taught that derivatization of proteins with PEG has been shown to increase circulating half life of the protein and to decrease immunogenicity *in vivo* (see page 320). It is noted that Applicants have not addressed these teachings of Miles *et al.* that relevant to the instant rejection.
Similarly, the alternative secondary reference of Iwashita *et al.* taught a solution of hemoglobin which rendered stroma free by filtration using 0.22 um membranes and unltrafiltered (see 'Materials and Methods'; and pages 277 and 278). Iwashita *et al.* taught that the chemical modification of the stroma free hemoglobin by attachment to POE is done to extend the life time of hemoglobin in the circulation (see page 278). Rausch *et al.* was applied to document that a solution of endotoxin-free, stroma free hemoglobin was known in the art (see Examples). Feola *et al.* was applied to document that the use of a Posidyne® 0.20 micron filter to further remove microbial contaminants from hemoglobin preparations was routine and conventional in the art.

As set forth previously, given the identified need in the art to obtain safer therapeutics comprising purified hemoglobin solutions as taught by Miles *et al.*, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace Woghiren's protein solution with Miles' hemoglobin protein solution, Iwashita's stroma-free hemoglobin, or Rausch's endotoxin-free, stroma free hemoglobin solution in Woghiren's method to produce the method of the instant invention, with a reasonable expectation of success. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of producing a safer non-toxic hemoglobin solution for use as a therapeutic, because modification of hemoglobin solution by linking to POE was well known in the art to prevent toxicity as taught by Miles *et al.* and to advantageously increase its circulating half life *in vivo* as taught by Miles *et al.* Clearly, the method of preparing a chemically modified hemoglobin that is substantially free of contaminants comprising dissolving an aPEG in a solvent in which the aPEG is stabile, filtering the aPEG solution

to substantially reduce the level of contaminants, and combining the filtered aPEG solution with a hemoglobin solution is *prima facie* obvious over the prior art record.

In sum, Applicants appear to argue that the combination of references fails because the prior art does not have anticipatory references regarding all elements of the invention. The argument is not persuasive. It should be noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)*. At issue is whether the claimed method, as a whole, is obvious over the method of the prior art primary reference given the teachings of the secondary references. As explained above, Applicant's invention, as a whole, is *prima facie* obvious over the applied prior art of record. It should be noted that what would reasonably have been known and used by one of ordinary skill in the art need not be explicitly taught. See *In re Nilssen*, 851 F.2d 1401, 7 USPQ2d 1500 (Fed. Cir. 1988). The test of obviousness is not express suggestion of the claimed invention in any and all of the references, but rather what the references taken collectively would reasonably have suggested to those of ordinary skill in the art presumed to be familiar with them. *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). Obviousness does not require absolute predictability, (see *In re Lamberti*, 192 USPQ 278), but only a reasonable expectation of success (see *In re O'Farrell*, 7 USPQ 2d 1673, Fed. Cir. 1988).

The Office has clearly established a *prima facie* case of obviousness. Contrary to Applicants' contention, the cited references teach the present invention including the dissolving of the aPEG in a solvent in which it is stable, filtering the solution to obtain a purified solution, and then using the filtered aPEG solution to modify hemoglobin. The rejection(s) stand.

Remarks

8) Claims 12-19 stand rejected.

9) **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the

THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

11) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

12) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

July, 2004

S. DEVI, PH.D.
PRIMARY EXAMINER